Version showing Changes Made:

1. A method for treating cancer in a human patient, comprising:

a) implanting at or around the site of a tumor in the patient a first cell population containing alloactivated lymphocytes that are allogeneic to leukocytes in the patient; and

b) implanting at or around the site of a tumor in the patient a second cell population containing alloactivated lymphocytes that are allogeneic to leukocytes in the patient;

wherein step a) and step b) are separated by an interval of at least three days, whereby the treatment stimulates a response in the patient against the tumor.

12. [The method of claim 13,]

A method for treating cancer in a human patient, comprising:

a) implanting at or around the site of a tumor in the patient a first cell population containing alloactivated lymphocytes that are allogeneic to leukocytes in the patient; and

b) implanting at or around the site of a tumor in the patient a second cell population containing alloactivated lymphocytes that are allogeneic to leukocytes in the patient;

wherein step a) and step b) are separated by an interval of at least three days, and wherein the cancer is selected from the group consisting of melanoma, pancreatic cancer, liver cancer, colon cancer, prostate cancer, and breast cancer.

REMARKS

This paper is responsive to the Office Action October 24, 2000, which is the second non-final action on the merits of the application. Claims 1-20 are pending in this application, and stand variously rejected.

Applicant acknowledges with gratitude withdrawal of all rejections previously made under 35 USC § 112, and of Slavin et al. (U.S. Patent 5,928,639) as a prior-art reference.

Enclosed with this amendment is an Interview Summary of telephone interviews conducted with Examiner Stroup in September, 2001. The Office indicated that the application was in condition for allowance. However, this decision was withdrawn, and an Office Action was issued bearing a mailing date of September 29, 2001 (Paper No. 11). Further telephone interviews took place, and applicant's representative was informed that the Office Action would be voided, and the application would proceed to allowance. Applicant's representative and the owner of this invention are disappointed that the allowance has apparently been withdrawn a second time.

Reconsideration and allowance of the application in view of the amendments and remarks made in this paper is respectfully requested.

Request for expedited processing

Since the application has already been withdrawn from allowance twice, and since the present Office Action makes no objections that could not have been made at a previous time, applicant respectfully requests that all remaining matters be resolved and the application be processed for issuance as soon as possible.

Regarding claim amendments

The amendment to claim 1 is supported at various places throughout the specification, and by claims 3 and 4 as originally filed. The amendment to claim 13 rewrites the claim in independent format, incorporating the limitations from claim 1 from which it previously depended. Accordingly, claim 13 as amended has not changed in subject matter or scope, and

is entitled to protection for all equivalent subject matter. No new matter is added to the claims as a result of entering these amendments. The amendments do not represent a dedication to the public of any subject matter disclosed in the specification or previously claimed.

Prior art rejections

Claims 1-10, 12-16 and 18-20 stand rejected under 35 USC § 102(b) or alternatively under 35 USC § 103(a) as obvious over Granger (U.S. Patent 5,837,233). The Office contends that since the Granger patent shows that implanting alloactivated lymphocytes into a tumor is effective in reducing tumor mass over periods of 58-74 weeks, and that as a consequence, the artisan *would not be dissuaded* from administering a second dose to patients experiencing a relapse.

With the utmost respect, this is not the legal standard for supporting a rejection under 35 USC § 102. The burden is not upon the applicant to show how the reference dissuades the reader from altering the teachings of the reference to arrive at the claimed invention. Rather, the burden is upon the Office to show how the reference or the related art affirmatively suggests the claimed invention. Should this rejection be maintained, applicant hereby requests that the Office provide an Examiner's Affidavit to support the contention of how it would be obvious to give two administrations of the Granger composition to arrive at the invention claimed in the present application.

A secondary reference by Fleshner et al. (Cell Transplantation 1:307, 1992) is put forward in the Office Action to support the general proposition that when the efficacy of a cancer therapy subsides then another treatment or dose is administered.

Applicant respectfully disagrees. Naturally, no responsible clinician would abandon all hope as soon as there is an indication that the first treatment has failed, and leave the patient to succumb to the illness. Instead, it is standard practice in clinical medicine to adjust treatment in accordance with the patient's response. However, this general principle does not provide motivation for administering multiple doses for treatments not previously believed to require multiple doses — such as the invention described in the Granger patent. In fact, there are at least 4 reasons why a clinician would not be motivated to administer alloactivated cells into a

tumor bed on more than one occasion, except for the teaching provided in the present invention.

First, as the Office Action points out, the Granger patent teaches that the efficacy of the composition is believed to relate to its immunostimulatory effect. Evidence that the treatment is effective over 58-74 weeks indicates an ongoing long-standing immune response, consistent with ongoing stimulation of immune memory cells by tumor antigen. Loss of effectiveness at the end of this long period strongly suggests that the treatment can no longer be effective — because the patient is now unresponsive, because they can no longer overcome tolerance, or because the tumor has become resistant to immune effector mechanisms (e.g., by shedding tumor antigen). Failure after such a long period of time logically leads to the conclusion that the modality is no longer effective, and that another type of cancer treatment should be substituted instead — as taught in the Fleshner reference.

Second, the clinician would not be motivated to give a second dose of the Granger composition, *because the clinical situation is not the same.* Granger teaches that alloactivated cells are planted into the tumor bed *at the time the primary tumor is removed by surgery.* If the tumor has been fully ressected through the course of the first intervention, then *there is no tumor mass or tumor site in which to administer a second dose*, except in the unfortunate circumstance that the cancer recurs. But with the teachings of the present invention, the skilled clinician will appreciate that the invention can also be practiced by leaving a small remnant of the tumor in place to receive the second dose, or place the second dose into a secondary or metastatic tumor, or go to the trouble of performing a surgical procedure to access a tumor that is not ressectable, for the purpose of giving two doses and obtaining the beneficial effect therefrom (see Example 8).

Third, the present application directs the clinician to consider administering a second dose of alloactivated cells into the tumor bed *well before there is evidence of failure of the first dose* — even if the procedure is complicated and expensive, as in the case of unressectable pancreatic cancer (Example 8). The time interval is typically chosen to optimize the immune reaction by the patient against the tumor, and is typically well before the 58-74 week period indicated in the Office Action. Without intending any limitation on the practice of the

invention, the applicant believes that early administration of the second dose can be important in maximizing the response before the immune system becomes refractory to stimulation for tumor-associated antigen.

Fourth, the subject application provides motivation required to administer two doses of allogeneic cells into the tumor bed, which is beyond just an additive effect expected for two subsequent doses. The synergistic effect is explained in detail on pages 8-11 of the specification, and illustrated in Examples 6 and 7. Animals that had received two administrations of alloactivated cells into their tumors (Groups 3 and 4) were compared with untreated animals (Group 1) and animals that had received only one dose (Group 2). The following results were obtained:

- Three of the five animals in Group 3 completely eliminated their tumors within 17 days of the second implant (Figure 5 and Table 6). Thus, at least **60%** of the treated subjects showed substantial regression of the tumor in size.
- Two of the five animals in Group 4 completely eliminated their tumors within 17 days of the second implant (Table 6). Thus, at least **40%** of the treated subjects showed substantial regression of the tumor in size.
- Three of the four animals that did not eliminate their tumor, but had the tumor surgically removed, showed lack of recurrence of a tumor after removal (Table 7) — a **75%** response rate.
- Two of the four animals that had the tumor surgically removed rejected a rechallenge by the D74 tumor line (Table 7). Thus, animals were resistant to a challenge akin to tumor metastasis at a frequency of **50%** of the animals.
- At least 8 of the 10 animals in the groups treated according to the invention (Groups 3 and 4) responded according to at least one of the criteria recited in claims 9 and 15 — a response rate of at least **80%**.

For any and all these reasons, the claimed invention is patentable over U.S. Patent 5,837,233. The Granger does not teach or fairly suggest administering two doses of alloactivated cells into the tumor site — rather, it teaches that a single administration is all that

is needed for the effects described. In contrast, the present disclosure provides special rationale for administering two doses early in treatment.

Withdrawal of this rejection is respectfully requested.

Claims 1-9 and 13-15 stand rejected under 35 USC § 102(b) as anticipated by Kruse et al. (Proc. Natl. Acad. Sci. USA 87:9377, 1990) and Kruse et al. (Proc. Am. Assoc. Cancer Res. 36:474, 1995).

Applicant respectfully disagrees. The first reference does not qualify as § 102(b) art, since it does not teach the treatment of humans. The second reference is an abstract that is inadequate to place the invention claimed in the present application in the hands of the public.

Furthermore, the Office has already recognized the difference between the technology described by Kruse and her colleagues, and the technology for implanting alloactivated cells into a tumor bed to elicit a host response. These and other articles published by Kruse et al. are discussed extensively in the Background section of the specification (pages 3-5). The technology involves generating cytotoxic T lymphocytes (CTL), which are effector cells that are designed to have a direct killing effect when administered to tumor cells (see abstract of the PNAS reference). To generate enough CTL for human therapy, donor cells are cultured with stimulator cells for about 3 weeks in the presence of IL-2, producing highly enriched end-stage effector cells. Ongoing treatment involved 1 to 5 treatment cycles every other month, with each cycle consisting of 2-3 CTL infusates within a 1 or 2 week period.

In contrast, the invention provided in the Granger patent and in the present application relates to cells that are not selected for their cancer killing potential, but for their potential to recruit an active response by the host. The Granger disclosure illustrates that a single is all that is needed to generate a therapeutic response.

The Office has issued two patents to the Granger technology. Each of the following features alone was considered to distinguish the Granger invention from the Kruse invention:

1. The alloactivated cells have the ability to stimulate a response by the host against the tumor;
2. The cells are harvested from culture during the initial stage of activation;
3. The cells can be used for treating tumors in sites that are not immunologically privileged, such as melanoma, pancreatic cancer, liver cancer, colon cancer prostate cancer, and breast cancer.

All of the claims pending in this application recite at least one of these limitations:

- Limitation 1 appears in claims 1-4, and 13, and their dependents
- Limitation 2 appears in claim 11, 17, and their dependents
- Limitation 3 appears in claim 12, 18, and their dependents

Since this covers all pending claims in this application, the claimed invention is distinguished from anything taught or suggested by Kruse et al.

It is respectfully noted that the Granger patent and the Kruse references cannot properly be combined under 35 USC § 103, to suggest that the Granger invention to be given in multiple doses. Even if a combination of references teaches every element of a claimed invention, without a motivation to combine the references, a rejection based on a prima facie case of obviousness is improper. *In re Rouffet,* 47 USPQ2d 1453 (Fed. Cir. 1998). The references are not combinable because the respective compositions have a very different purpose — the Granger composition to stimulate a host anti-tumor response, the Kruse composition to have a direct tumor-killing effect.

Withdrawal of this rejection is respectfully requested.

Claims 11 and 17 stand rejected under 35 USC § 103(a) as being unpatentable in view of the Granger patent in combination with two other cited references. Applicants do not acquiesce to the arguments made in the Office Action. However, no response needs to be made, since the arguments already presented are sufficient to remove Granger as a reference for the claimed invention.

Conclusion

Applicant requests that all outstanding rejections be reconsidered and withdrawn in light of this submission. The application is believed to be in condition for allowance, and an early Notice of Allowance is respectfully requested.

In the event that the Examiner determines that there are other matters to be addressed, she is invited to contact applicants' representative for further discussion .

Should the Patent Office determine that a further extension of time or other relief is required for further consideration of this application, applicant hereby petitions for such relief and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of this document to the Credit Card indicated on accompanying PTO-2038.

Respectfully submitted,

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